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Aggressiveness of 'true' interval invasive ductal carcinomas of the breast in postmenopausal women

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There is debate whether interval carcinomas differ from screen-detected tumours biologically. In this study, clinico-pathological parameters and the expression of well-validated biological markers were compared between 'true' interval carcinomas and screen-detected/missed carcinomas hypothesising that 'true' interval carcinomas show a more aggressive biological behaviour. The study group consisted of 92 consecutive postmenopausal women attending the breast screening programme and presenting with an invasive ductal carcinoma. All screening mammograms were re-reviewed. Sixteen patients had a 'true' interval carcinoma. Seven carcinomas were missed at screening, but detected on re-reviewing of the screening mammogram. Radiological characteristics were assessed from diagnostic mammograms. Data on patient- and tumour characteristics and follow-up data were recorded from hospital records. Median follow-up was 61 months. Immunohistochemistry for ER, PR, Her2/neu and p53 was performed on TMA sections. Univariate and multivariate logistic regression analyses were performed. In univariate analysis, 'true' interval carcinomas were significantly larger (odd ratios (OR) 7.2, 95% CI 1.8–28.1) and less frequently ER (OR 0.3, 95% CI 0.1–0.9) and PR (OR 0.3, 95% CI 0.1–1.0) positive. In multivariate analysis, 'true' interval carcinoma was independently associated with larger tumours (OR 7.0, 95% CI 1.4–36.2). A trend toward ER negativity was found (OR 0.3, 95% CI 0.1–1.1). 'True' interval carcinomas showed a trend toward a decreased relapse-free survival (HR 1.7 95% CI 0.9–3.1). Although 'true' interval carcinomas were significantly larger than screen-detected/missed interval carcinomas, it remains challenging to observe parameters that determine this difference between 'true' interval carcinomas and screen-detected lesions.
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Keywords: breast cancer; breast cancer screening; interval carcinoma; tumour progression; follow-up

From 1989 till 1997, a nationwide breast cancer screening programme has gradually been implemented in the Netherlands.[1] Starting as a biennial screening mammography for women aged 50–69, in 1999 the programme was also offered to women aged 70–75 years. The attendance rate is over 80% in the northern part of the Netherlands. The introduction of the screening programme has led to a substantial decrease in the rate of advanced breast carcinoma and to a breast cancer mortality decline of almost 30% in the screened and non-screened population.[2] In spite of the participation in the screening programme, a number of women still

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present with a clinically symptomatic carcinoma between two screening moments, a so-called interval carcinoma. In participants in the Dutch Breast Cancer Screening Programme, 36% of the tumours emerge as interval carcinomas[3] and there is discussion whether interval carcinomas differ from screen-detected tumours biologically and should therefore deserve a different, perhaps more aggressive treatment.[4] Over the years many studies have been conducted on the differences between interval- and screen-detected carcinomas.[5–16] Comparison of these studies is difficult, because of the great heterogeneity in screening group, screening interval and study design. Therefore, in this analysis a very homogeneous group of postmenopausal women is studied. All women presented with an invasive ductal carcinoma and participated in the breast screening programme (as confirmed by the Northern Netherlands Comprehensive Cancer Centre). The patients' screening mammograms were re-reviewed to differentiate between 'true' interval carcinomas and false-negative mammograms (missed carcinomas). We studied the expression of conventional tumour progression-related biological markers (oestrogen receptor (ER), progesterone receptor (PR), HER2/neu and p53), radiological characteristics (breast density, tumour outlining and calcifications) and follow-up data hypothesising that if 'true' interval carcinomas are indeed a more aggressive subgroup of carcinomas, these variables differ between both groups.

Materials and methods

Definitions

Screen-detected carcinoma: a carcinoma detected in the screening programme.

'Missed' carcinoma: a clinically detected carcinoma that occurred between two screening moments with a visible lesion on re-reviewing of the screening mammogram.

Interval carcinoma: a clinically detected carcinoma that occurred between two screening moments after a 'true' negative screening mammogram.

Patients

A total of 99 consecutive postmenopausal women from whom participation in the biannual breast screening programme could be confirmed by the Northern Netherlands Comprehensive Cancer Centre and who were treated between 01 January 1996 and 31 December 2001 at the University Medical Centre Groningen for a primary operable invasive ductal carcinoma of the breast as defined by the WHO classification[17] were retrospectively included in this study. Seven patients were excluded; one patient because she was already in clinical follow-up for an earlier *in situ* lesion and six patients because their screening mammograms were not available for re-reviewing. Therefore, the patient and tumour characteristics and data on follow-up were obtained retrospectively from hospital records and are summarised in Table 1. Histology was reviewed on the original haematoxylin- and eosin-stained section. The median follow-up was 61

Table 1 Patient and tumour characteristics

	n	%
Age at diagnosis		
Median (range)	60.2	50.2–74.8
Detection		
Screen detected	69	75
Interval ('true')	16	17.4
Missed	7	7.6
Mammographic breast density on diagnostic mammography (BIRADS)		
I	30	32.6
II	19	20.7
III	23	25.0
IV	16	17.4
Calcifications on screening mammography		
None	63	68.5
Cluster	6	6.5
Linear	1	1.1
Granular	18	19.6
Linear+granular	3	3.3
Branching	1	1.1
Outlining on screening mammography		
Not visible	22	24.2
Sharp	5	5.5
Unsharp	39	42.9
Spiculae	22	24.2
Unsharp+spiculae	3	3.3
Therapy		
BCT	54	58.7
Mastectomy	38	41.3
Axillary nodal status		
Negative	61	66.3
Positive	30	32.6
Not assessed	1	1.1
Pathological tumour size		
<2 cm	52	56.5
$>2-<5$ cm	34	37.0
>5 cm	6	6.5
Grade of differentiation		
Well	26	28.3
Moderate	43	46.7
Poor	22	23.9
Missing	1	1.1
Adjuvant chemotherapy		
Yes	30	32.6
No	62	67.4
Adjuvant radiotherapy		
Yes	63	68.5
No	29	31.5

BCT, breast conserving therapy; cm, centimetre; *n*, number of cases; %, percentage.

months (range 6.3–106.4). Follow-up was performed according the follow-up guidelines of the Northern Netherlands Comprehensive Cancer Centre and consisted of a yearly mammogram in the first 5 years of follow-up and clinical examination (quarterly in the first year of follow-up, biannually in the second year and annually in the third to fifth year. After 5 years, patients were referred back to the screening programme.[18] During follow-up, four patients developed a local recurrence after a median follow-up of 26.7 months. Eleven patients developed distant metastasis after a median follow-up of 27.3 months. In total, 14 patients presented with a relapse with a median relapse-free survival of 26.2 months. Five patients died related to breast cancer with a median overall survival of 28.6 months.

Re-reviewing of Mammograms

The original screening mammogram of all patients was re-reviewed by two of the investigators (GJdH and RP), who are both experienced screening radiologists, to differentiate between 'true' interval carcinomas and interval carcinomas as a result of a false-negative screening mammogram (missed carcinomas). A consensus reading was performed. The following criteria were used: type 1, nothing to be observed; type 2, minimal signs only in retrospect; type 3, significant abnormality. Type 3 tumours were considered missed carcinomas. There was a maximum bias because both radiologists knew the inclusion criteria and question of the study. Breast density was scored on clinical mammograms by one of the investigators (RP) using the Breast Imaging Reporting and Data Systems (BIRADS) classification for breast density.[19]

Tissue Microarray Construction

From the patient's tumour paraffin block, three 0.6-mm core samples of the most representative tumour area were included in a tissue microarray. The technique of tissue microarray production has been described and validated for breast carcinoma by others.[20,21] In brief, the most representative tumour area was marked on the original haematoxylin- and eosin-stained section. Using this section as an orientation, three 0.6-mm core punches were taken from the selected area in the donor blocks and mounted in a recipient block, using a manual tissue microarray device (Beecher Instruments, Silver Springs, MD, USA).

Immunohistochemistry

Immunohistochemistry for ER, PR, Her2/neu and p53 was performed on sections from the tissue array. The antibodies and antigen retrieval methods used are summarized in Table 2. The immunostaining protocol was as follows: sections were deparafinized in pure xylene, rehydrated in decreasing concentrations of ethanol and washed in distilled water. Antigen retrieval was performed. The endogenous peroxidase reaction was blocked by incubating in 3% perhydrol for 30 min. The primary antibody diluted in PBS containing 1% bovine serum albumin (BSA) was incubated for 1 h, after which the secondary (biotinylated rabbit anti mouse, DAKO, 1:100 diluted in PBS containing 1% BSA and 1% AB-serum) and tertiary (biotinylated swine anti rabbit, DAKO, 1:100 diluted in PBS containing 1% BSA and 1% AB-serum) antibodies were incubated for 30 min each. Visualisation was performed using the diaminobenzidine tetrahydrochloride/peroxidase reaction. Counterstaining was performed using haematoxylin. Sections were dehydrated using rising concentrations of alcohol and were mounted.

Evaluation of Immunohistochemistry

Antibody staining was scored by one investigator (BvdV), under supervision of an experienced breast pathologist (JW), who randomly verified the scoring. ER, PR and p53 were graded based on the percentage of tumour cells showing positive nuclear staining. ER and PR were considered positive if nuclear staining was present in $>10\%$ of the cells, and p53 was considered positive in case of a substantial percentage of positively stained nuclei ($>30\%$). Her-2/neu expression was graded as recommended by the HercepTest scoring guidelines: 0: no staining at all or membrane staining in $<10\%$ of the tumour cells; 1+: a faint/barely perceptible partial membrane staining in $>10\%$ of the tumour cells; 2+: weak-to-moderate complete membrane staining in $>10\%$ of the tumour cells; 3+: strong complete membrane staining in $>10\%$. Her-2/neu was considered to be overexpressed if the score was 3+.

Table 2 Antibodies and antigen retrieval methods

Antibody	*Clone*	*Supplier*	*Dilution*	*Antigen retrieval*
ER	6F11	Ventana	[a]	Tris/HCL 0.1 M (pH 9.5) 30′ 98 °C microwave
PR	1A6	Ventana	[a]	Tris/HCL 0.1 M (pH 9.5) 30′ 98 °C microwave
Her2/neu	CB11	Ventana	[a]	Tris/HCL 0.1 M (pH 9.5) 30′ 98 °C microwave
p53	BP-53-12-1	Biogenix	1:800	Tris/HCL 0.1 M (pH 9.5) 30′ 98 °C microwave

[a]Prediluted by supplier.

Data Analysis

Data analysis was performed using the SPSS 14.0.2 statistical package (SPSS, Chicago, IL, USA). An univariate logistic regression analysis was performed to assess the odd ratios (OR) of clinico-pathological variables and biomarkers in 'true' interval carcinoma *versus* screen-detected/missed carcinoma. All parameters with an OR of 3.0 or higher in the univariate logistic regression analysis were then entered into a stepwise multivariate logistic regression analysis. A Cox regression analysis was performed to assess relapse-free and overall survival in 'true' interval carcinoma *versus* screen-detected/missed carcinoma.

Results

Tissue cores from all cases were successfully included in the TMA. Immunohistochemistry was assessable in 90 cases (98.0%) for p53, in 88 (96.0%) for Her2/neu and ER, and in 87 cases (95%) for PR.

The results from the re-reviewing of the mammograms are shown in Table 1. In all, 16 of the 23 cases marked as interval carcinomas, were retrospectively 'true' interval carcinomas. Seven cases showed a retrospectively visible lesion on the screening mammogram. A majority of those lesions (5/7) were now classified as 'uncertain benign' in which they had earlier been classified as 'benign'. Two cases were now classified as 'malignancy suspected'. One of those cases had originated in very dense breast tissue, which might have caused the judgement error. A clinical mammogram was available in 88 cases (96%). Breast density was evenly distributed between 'true' interval carcinomas and screen-detected/missed carcinomas.

Univariate Analysis

The results of univariate logistic regression analyses of clinico-pathological parameters and biomarkers in 'true' interval- *versus* screen-detected/missed carcinomas are shown in Table 3. A majority of these parameters did not differ between both groups. 'True' interval carcinomas were significantly larger (OR 7.2, 95% CI 1.8–28.1, $P=0.005$) and were less often ER positive (OR 0.3, 95% CI 0.08–0.9, $P=0.034$). A trend toward PR negativity (OR 0.3, 95% CI 0.1–1.0, $P=0.06$) was found in 'true' interval carcinomas.

Multivariate Analysis

Table 4 shows the results of a multivariate analysis. Tumour size was significantly associated with 'true' interval carcinoma (HR 5.1, 95% CI 1.2–21.0, $P=0.02$). A trend toward ER negativity was also found (HR 0.3, 95% CI 0.08–1.2, $P=0.08$). PR was eliminated from the equation.

Table 3 Univariate logistic regression analysis of clinico-pathological variables and biological markers in 'true' interval carcinoma *versus* screen-detected/missed carcinoma

	'True' interval carcinoma OR (95% CI)	P
Age at diagnosis ($n=92$)	1.0 (0.9–1.1)	0.808
Mammographic density (BIRADS) (n = *88*)		
I	1	
II	0.5 (0.1–2.6)	0.389
III	0.6 (0.1–2.7)	0.507
IV	1.3 (0.3–5.6)	0.696
Mammographic calcifications (n = *92*)		
Yes	1	
No	1.5 (0.4–5.0)	0.538
Treatment (n = *92*)		
BCT	1	
Mastectomy	1.5 (0.5–4.5)	0.439
Axillary nodal status (n = *91*)		
Negative	1	
Positive	2.4 (0.8–7.2)	0.117
Tumour size (n = *88*)		
<2 cm	1	
>2 cm	7.2 (1.8–28.1)	0.005
Grade of differentiation (n = *91*)		
Well	1	
Moderate	0.4 (0.1–1.8)	0.244
Poor	2.0 (0.5–7.4)	0.320
Estrogen receptor (n = *88*)		
Negative	1	
Positive	0.3 (0.1–0.9)	0.034
Progesterone receptor (n = *87*)		
Negative	1	
Positive	0.3 (0.1–1.0)	0.06
Her2/neu (n = *88*)		
0/1/2	1	
3	1.6 (0.3–8.6)	0.603
P53 (n = *90*)		
Negative	1	
Positive	1.6 (0.2–16.2)	0.701

BCT, breast conserving therapy; cm, centimetre; 95% CI, 95% confidence interval; HR, hazard ratio; *P*, significance.

Clinical Outcome

The Cox regression analysis showed a trend toward decreased relapse-free survival in 'true' interval carcinomas (Table 5). No difference in overall survival was found.

Discussion

This study compared clinical, pathological and radiological variables, the expression of conventional biomarkers and follow-up data of 'true' interval

Table 4 Independent predictors of 'true' interval carcinoma ($n = 82$)

Parameters	*OR*	*95% CI*	P-*value*
Tumour size			
<2 cm	1		
>2 cm	5.1	1.2–21.0	0.02
Estrogen receptor			
Negative	1		
Positive	0.3	0.1–1.2	0.08

cm, centimetre; 95% CI, 95% confidence interval; OR, odds ratio.
Regression analysis by elimination of variables in a stepwise manner.

Table 5 Relapse-free and overall survival for 'true' interval carcinoma *versus* screen-detected/missed carcinoma

	HR	*95% CI*	P-*value*
*Relapse-free survival (*n = *91)*			
SD/M carcinoma	1		
'True' interval carcinoma	1.7	0.9–3.1	0.08
*Overall survival (*n = *88)*			
SD/M carcinoma	1		
'True' interval carcinoma	1.3	0.1–11.6	0.82

95% CI, 95% confidence interval; HR, hazard ratio; SD/M, screen-detected and missed carcinomas.
Cox regression analysis.

carcinomas *versus* screen-detected and missed carcinomas, hypothesising that 'true' interval carcinomas express parameters of aggressive behaviour more abundantly. 'True' interval carcinomas were larger and showed a trend toward ER negativity and decreased relapse-free survival.

In Table 6, the results from a literature search on studies assessing differences between interval- and screen-detected breast carcinomas conducted in postmenopausal women are shown. When comparing the results from the studies that defined 'true' interval carcinoma with this study, our finding of increased tumour size and decreased ER expression in 'true' interval carcinoma confirms some of the results of those studies. Some studies also found differences in the number of positive axillary lymph nodes and tumour grade, findings that we could not confirm. Those findings were never confirmed in multivariate analysis however.

Several restrictions apply when comparing studies conducted on the differences between interval- and screen-detected carcinomas. First, there is large heterogeneity in study groups, screening interval, type of breast cancer studied and study design. Second, most studies, including the current one, comprise a small study group. One might argue that these study groups are too small and heterogeneous to gain sufficient statistical power to observe differences between screen-detected and interval carcinomas. To avoid heterogeneity in type of breast carcinomas and the patient population studied, we focused on postmenopausal women in the screening programme, presenting with an invasive ductal carcinoma as defined by the WHO classification,[17] as this is by far the most common type of breast cancer. Third, most studies use univariate logistic regression analysis to study differences, making their findings more susceptible to biases.[22] Therefore, we performed a stepwise multivariate logistic regression analysis to correct for confounding factors. Fourth, the definition of an interval carcinoma differs between studies. Some investigators define all carcinomas detected clinically between two screening moments as an interval carcinoma. This is a correct definition of interval carcinoma when looking at the sensitivity of the screening programme as a whole. A portion of those interval carcinomas, however, are in fact significant lesions that should have been referred. These tumours are not detected in the interval between two screening moments because of their biological behaviour, but due to restrictions of the screening programme. Therefore, in this study screening mammograms were re-reviewed to differentiate between 'true' interval carcinomas and interval carcinomas as a result of a false-negative screening mammogram. We defined an interval carcinoma as a clinically detected carcinoma that occurred between two screening moments after a 'true' negative screening mammogram. Using this definition of interval carcinoma, the sensitivity of the screening mammogram as a test for detecting breast carcinoma can be assessed. The programme sensitivity of the Dutch screening programme was 65% in the nationwide evaluation of the programme (meaning that for every two carcinomas discovered in the screening programme in the 2 years between screening moments another carcinoma is discovered clinically). In our series, the programme sensitivity was 75% (using the first definition described above). It is plausible that this difference is caused by the selection of the study group (only invasive ductal carcinomas were included). The Dutch National Evaluation Team Breast Cancer Screening (LETB) has estimated that in general (ductal carcinoma *in situ* and lobular carcinoma included) from all the interval carcinomas approximately 50% is a 'true' interval carcinoma. Approximately 25% of the interval carcinomas show a clear lesion, for which a patient should have been referred for additional diagnostics, on re-reviewing of the screening mammography, and a further 25% show 'minimal signs', that are only suspicious with the knowledge of a clinically discovered interval carcinoma. The percentage of 'true' interval carcinomas in this series was 30.4%, which is comparable to those estimations.

'True' interval carcinomas were five times more often larger sized (>2 cm) tumours in our series. Several explanations for the increased size of interval carcinomas have been suggested in literature. First, interval carcinomas have been associated with dense breast tissue, with poor outlining and with absence of calcifications on mammography.[12,23,24]

Table 6 Significant differences between interval- and screen-detected tumours from literature

Author (year)	*Number of screen-detected carcinomas*	*Number of interval carcinomas*	*Age groups*	*Screening interval (years)*	*'True' interval carcinoma?*	*Analysis (univariate/ multivariate)*	*Significant differences*
DeGroote *et al* (1983)[8]	99	21	30–80	1	Yes	Univariate	Number of positive axillary lymph nodes Overall mortality 6-year survival
Heuser *et al* (1984)[12]	32	28	—	1	No	Univariate	Calcifications on mammography Age Survival
Frisell *et al* (1987)[9]	222	60	40–64	2	Yes	Univariate	Tumour stage ER expression
Hatschek *et al* (1989)[11]	212	98	40–74	2	No	Univariate	S-phase fraction
Bahnsen *et al* (1994)[5]	163	22	36–75	2	No	Univariate	Number of positive axillary lymph nodes
Burrell *et al* (1996)[6]	267	82	50–64	Varying	Yes	Univariate	Tumour size Tumour grade Number of positive axillary lymph nodes
Klemi *et al* (1997)[13]	385	100	40–74	Varying	No	Univariate[a]	S-phase fraction Age Stage
Crosier *et al* (1999)[7]	84	51	50–64	3	Yes	Univariate	Tumour size Tumour grade ER expression Her2/neu expression p53 expression ki-67 expression
						Multivariate	ki-67 expression Her2/neu expression
Porter *et al* (1999)[14]	279	150	40–>80	Varying	No	Univariate[b]	Mitotic count Tumour grade ki-67 expression ER expression
Gilliland *et al* (2000)[10]	64	63	40–80	Varying	No	Univariate	Proportion of proliferating cells p53 expression Number of apoptotic cells
						Multivariate	p53 expression ki-67 expression
Raja *et al* (2001)[15]	625	230	50–64	3	Yes	Univariate	Tumour grade Tumour size Number of positive axillary lymph nodes
Shen *et al* (2005)[16]	712	280	40–64	1	No	Multivariate	Breast cancer-related death
This study	63	36	50–74	2	Yes	Univariate	Tumour size ER expression
						Multivariate	Tumour size

[a]Adjusted for tumour size.
[b]Adjusted for age and tumour size.

When tumours from women with dense breasts become clinically apparent after a negative screening mammogram, they are more ahead in their natural history compared with screen-detected carcinomas and are therefore larger, a phenomenon called lead time bias.[25] In our series, breast density was evenly distributed between screen-detected/missed carcinomas and 'true' interval carcinomas. Second, several studies suggest that interval carcinomas are rapidly proliferating tumours. Several different parameters for proliferation are used in these studies. Two studies found increased mitotic count and Ki-67 antigen expression in interval carcinomas.[7,10] One of those studies, however, was performed a heterogeneous group of breast carcinomas, including lobular carcinomas, which may have confounded the results of this study somewhat. Ki-67 immunohistochemistry was not performed in this series, because this expression is very heterogeneous in ductal breast carcinoma and therefore difficult to interpret on TMA. Others used fraction of tumour cells in the S-phase fraction of the cell cycle as a marker for proliferation and found an increase of this fraction in interval carcinomas.[11,13] In this

study, we used the Bloom–Richardson scoring system, of which mitotic count is a part, to assess grade of differentiation as a marker for proliferation.[26] We did not observe a difference between both groups of this study. There are other biological factors outside proliferation rate that may have a role in the development of breast carcinoma and may explain the difference in size between 'true' interval- and screen-detected/missed carcinoma. For example, tumour cells from 'true' interval carcinomas may be less susceptible to apoptosis. One study assessing the number of apoptotic cells in interval- and screen-detected carcinomas did not observe a difference between both groups.[10] In addition, tumours that have a higher angiogenic potential may grow faster because of reduced tumour cell death. Another key role player is the amount of tumour stroma induced that will affect significantly the size of tumours, especially of invasive ductal carcinomas, which are known for their highly variable desmoplasia inducing potential.[27] It remains to be established if and to which extent these explanations contribute to the difference in growth rate between screen-detected carcinomas/missed carcinomas and 'true' interval carcinomas.

It is assumed that 50–75% of the tumours discovered in the first screening round are small, biologically indolent tumours.[28–30] These tumours are more often ER and PR positive. We found that screen-detected/missed carcinomas were significantly more often ER positive in univariate analysis, a result that is confirmed by other studies.[7] This association only showed a trend toward significance in multivariate analysis, probably because of the relatively small sample size of this study. These relatively less aggressive tumours might also explain the trend toward increased relapse-free survival we found for screen-detected carcinomas.

In conclusion, in this small consecutive and homogeneous study group of postmenopausal women with invasive ductal breast carcinoma, we found a significant difference in tumour size between 'true' interval- *versus* screen-detected/missed carcinomas in multivariate analysis. ER expression differed significantly between both groups in univariate analysis. It remains challenging, however, to observe parameters that determine this difference between the 'true' interval carcinomas and screen-detected lesions.

Disclosure/conflict of interest

The authors declare no conflict of interest.

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